CELL MIGRATION

The mechanics of group travel

Substrate stiffness influences single cell migration, but its effect on collective cell migration is less clear. Ng *et al.* now show that substrate stiffness regulates the migration of epithelial cell sheets, and that this mechanoresponse is mediated by myosin II and depends on cadherin-mediated cell adhesion.

The authors developed a wound healing assay in which substrate stiffness could be altered, and they observed that cell sheets migrated further on stiffer substrates than on softer ones. Moreover, the migration speed of individual cells within the sheet, and their directionality towards the wound, increased with increasing stiffness. Cells also migrated more persistently on stiffer substrates. Thus, substrate stiffness enhances the speed, directionality and persistence of collective cell migration. Importantly, the authors also found that neighbouring cells within epithelial sheets coordinate their movement in response to mechanical cues.

Next, they characterized the physiological and molecular events that accompany increased collective cell migration on stiffer substrates. On stiff substrates most cells at the wound edge, and in several rows behind this, were polarized, as judged by the position of labelled Golgi, and lamellipodial protrusions extended largely towards the wound, even on cells behind the wound edge. By contrast, on soft substrates, although cells at the wound edge were polarized, Golgi orientation and lamellipodial extensions were less uniform in those immediately behind. At the molecular level the authors observed a similar difference between cells on stiff and soft substrates in an activation gradient of myosin II (this motor protein is known to be influenced by substrate stiffness and to regulate cell migration in single cells). On stiff substrates overall myosin II activity was higher than on soft substrates, and myosin II activation was present significantly further into the epithelial sheet. Reducing myosin II activity, using a chemical inhibitor or RNAi, decreased the speed of collective cell migration on stiff substrates and also cell–cell coordination. Thus, myosin II mediates the response of collectively migrating cells to substrate stiffness.

Finally, the authors asked whether cell–cell adhesion has a role in enhancing collective cell migration on stiffer substrates. Disruption of adherens junctions, using RNAi against junction components, reduced the effect of substrate stiffness on cell–cell coordination during collective cell migration, and the levels of active myosin II were reduced with increasing distance from the wound edge. Thus, cell–cell adhesion is necessary to relay mechanosensory responses of cells at the wound edge into the sheet, where they activate myosin II in a stiffness-dependent fashion.

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